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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification : Not classified

A2

(11) International Publication Number: **WO 00/41463**

(43) International Publication Date: 20 July 2000 (20.07.00)

(21) International Application Number: PCT/EP99/10295

(22) International Filing Date: 21 December 1999 (21.12.99)

(30) Priority Data:
9900630.6 12 January 1999 (12.01.99) GB

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL TREATMENT

(57) Abstract

This invention provides a pharmaceutical pack comprising as active ingredients (1) an antiviral agent active against hepatitis B virus and (2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection, the active ingredients being for simultaneous or sequential use. Preferred components are a nucleoside analogue as the antiviral agent, together with a hepatitis B virus vaccine which comprises a hepatitis B virus surface antigen.

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NOVEL TREATMENT

This invention relates to the use of a nucleoside analogue active against hepatitis B virus (HBV), or another class of antiviral active against HBV, such as γ interferon or a nucleotide analogue and an HBV vaccine in the treatment of hepatitis B virus infections.

Chronic hepatitis B virus (HBV) infection, for which there is currently no effective cure, constitutes a global public health problem of enormous dimensions. Chronic carriers of HBV, estimated to number more than 300 million world-wide, are at risk for development of chronic active hepatitis, cirrhosis and primary heptocellular carcinoma.

EP-A-388049 (Beecham Group p.l.c.), discloses the use of penciclovir/famciclovir in the treatment of hepatitis B virus infection. All references herein to penciclovir/famciclovir include pharmaceutically acceptable salts, such as the hydrochloride, and solvates, such as hydrates.

EP-A-494119 (IAF Biochem. International Inc.) discloses the use of 1,3-oxathiolane nucleoside analogues, including lamivudine, in treatment of Hepatitis B.

The present invention provides a pharmaceutical pack comprising as active ingredients (1) an antiviral agent active against hepatitis B virus and (2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection, the active ingredients being for simultaneous or sequential use.

By pharmaceutical pack is meant a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Where the antiviral agent and the HBV vaccine are intended for administration as two separate compositions these may be presented in the form of, for example, a twin pack.

The invention may be used for either the treatment or prophylaxis of hepatitis B infections. The invention is most particularly of value for treatment, for example, of chronic hepatitis B infections.

In one aspect, the antiviral agent as used in the pharmaceutical pack is a nucleoside agent. In a further aspect the antiviral agent is a nucleotide agent. Suitable agents for use in the invention include penciclovir, famciclovir, lamivudine, ganciclovir, lobucavir, adefovir, ribavirin, BMS200,475, vidarabin or ARA-AMP. Preferred nucleoside analogues include penciclovir, famciclovir and lamivudine.

A further potential antiviral agent is an interferon. Alpha – interferon is especially preferred.

Information with respect to structure and activity of nucleoside analogues may be obtained from well known pharmaceutical industry references, such as "Pharmaprojects", PJB publications Limited, Richmond, Surrey, U.K. or from 'R & D Focus', isssued by IMS World publications, 364 Euston Road, London NW1 3BL.

References to an anti-hepatitis B virus nucleoside analogue, including the specific compounds mentioned hereinbefore and salts thereof, include solvates such as hydrates.

Examples of pharmaceutically acceptable salts are as described in the aforementioned Patent reference in the name of Beecham Group p.l.c. and references quoted therein, the subject matter of which are incorporated herein by reference.

It will be appreciated that the anti-hepatitis B virus nucleoside or nucleotide analogue and HBV vaccine of this invention may be administered in combination with other pharmacologically active agents, in particular, other antivirals.

In this invention the vaccine for the prophylaxis and/or treatment of hepatitis B infection includes all vaccines containing HBV antigens (such as surface antigen, core and polymerase) and therapeutic vaccines.

In one aspect of the invention the hepatitis B virus antigen is the hepatitis B surface antigen (HbsAg). The preparation of Hepatitis B surface antigen is well documented. See for example, Harford et. al. in Develop. Biol. Standard 54, page 125 (1983), Gregg et. al. in Biotechnology, 5, page 479 (1987), EP-A- 0 226 846, EP-A-0 299 108 and references therein.

As used herein the expression 'Hepatitis B surface antigen' or 'HBsAg' includes any HBsAg antigen or immunogenic derivative thereof, particularly fragments thereof, displaying the antigenicity of HBV surface antigen. It will be understood that in addition to the 226 amino acid sequence of the HBsAg S antigen (see Tiollais et. al. Nature, 317, 489 (1985) and references therein) HBsAg as herein described may, if desired, contain all or part of a pre-S sequence as described in the above references and in EP-A- 0 278 940. HBsAg as herein described can also refer to variants, for example the 'escape mutant' described in WO 91/14703. In a further aspect the HBsAg may comprise a protein described as L* in European Patent Application Number 0 414 374, that is to say a protein, the amino acid sequence of which consists of parts of the amino acid sequence of the hepatitis B virus large (L) protein (ad or ay subtype), characterised in that the amino acid sequence of the protein consists of either:

(a) residues 12 - 52, followed by residues 133 - 145, followed by residues 175 - 400 of the said L protein; or

(b) residue 12, followed by residues 14 - 52, followed by residues 133 - 145, followed by residues 175 - 400 of the said L protein.

HBsAg may also refer to polypeptides described in EP 0 198 474 or EP 0 304 578.

Normally the HBsAg will be in particle form. It may comprise S protein alone or may be as composite particles, for example (S, L*) wherein L* is as defined above and S denotes the S-protein of hepatitis B surface antigen.

A preferred hepatitis B antigen is this composite particle, defined as S,L*.

A further preferred hepatitis B antigen is the 226 amino acid sequence of the HBV surface antigen, in particle form.

Such a vaccine may advantageously include a pharmaceutically acceptable excipient such as a suitable adjuvant. Suitable adjuvants include an aluminium salt such as aluminium hydroxide gel (alum) or aluminium phosphate (as described in WO93/24148), but may also be a salt of calcium, iron or zinc, or may be an insoluble suspension of acylated tyrosine, or acylated sugars, cationically or anionically derivatised polysaccharides, or polyphosphazenes.

Advantageously, the hepatitis B virus may be formulated with strong adjuvant systems. Thus in the formulation of the invention, it is preferred that the adjuvant composition induces an immune response comprising TH1 aspects. Suitable adjuvant systems include, for example a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL) together with an aluminium salts. A vaccine comprising hepatitis B surface antigen in conjunction with 3D-MPL was described in European Patent Application 0 633 784.

An enhanced system involves the combination of monophosphoryl lipid A and a saponin derivative particularly the combination of QS21 and 3D-MPL as disclosed in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol as disclosed in WO 96/33739.

Other known adjuvants which may be included are CpG containing oligonucleotides (see University of Iowa; WO9602555).

In a preferred embodiment of the present invention there is provided a vaccine comprising an HBV antigen, adjuvanted with a monophosphoryl lipid A or derivative thereof.

Preferably the vaccine additional comprises a saponin, more preferably QS21.

Preferably the formulation additional comprises an oil in water emulsion and tocopherol.

A particularly potent adjuvant formulation involving QS21, 3D-MPL & tocopherol in an oil in water emulsion is described in WO 95/17210.

The present invention also provides a method of treatment and/or prophylaxis of hepatitis B virus infections, which comprises administering to a human or animal subject, suffering from or susceptible to Hepatitis B virus infection, either either simultaneously or sequentially in any order, a safe and effective amount of 1) an antiviral agent active against hepatitis B virus and 2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection.

The antiviral such as penciclovir/famciclovir and the HBV vaccine or a pharmaceutically acceptable salt or ester thereof, may be co-administered in the form of two separate pharmaceutical compositions for simultaneous or sequential use. Normally the active ingredients will be administered separately according to the normal dosage and administration regimen for the ingredients given alone. Commencement of administration may be either with the vaccine or the antiviral.

The present invention also provides for the use of an antiviral compound in the manufacture of a medicament for the treatment of patients already primed with a hepatitis B vaccine and suffering from a hepatitis B virus infection. The invention further provides for the use of a hepatitis B vaccine in the manufacture of a medicament for the treatment of patients already primed with an antiviral compound and suffering from a hepatitis B virus infection. The preferred antiviral is a nucleoside analogue, most preferably penciclovir/famciclovir or lamivudine. Preferred hepatitis B vaccines are identified hereinabove.

The unit doses of the nucleoside or nucleotide analogue may be administered, for example, 1 to 4 times per day. The exact dose will depend on the route of administration and the severity of the condition being treated, and it will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient and immunocompromised patients may require an increased dosage.

Vaccines are administered in multiple doses at various intervals. This is usually 6 - 12 doses at biweekly or monthly intervals.

The preferred ingredients in the pharmaceutical pack when administered simlutaneously are given as separate preparations, for example, as vaccinations in each arm. It is however possible to consider simultaneous administration by mixing the ingredients before administration. The ingredients may be given enterally, such as orally or parenterally (e.g. intramuscularly or, more particularly, intravenously).

The anitviral agents of the invention may be formulated as a tablet prepared by conventional means. Compositions for oral use such as tablets and capsules may be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, micro -crystalline cellulose or calcium hydrogen phosphate); lubricant (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agent (e.g. sodium lauryl sulphate). Tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives

(e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of one or both active ingredients.

For parenteral administration the compositions may be presented in a form suitable for bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in syringes, ampoules or in multi-dose containers, with an added preservative.

The active antiviral agent may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredients may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For rectal administration the active antiviral agents may be formulated as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The active antiviral agents of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the lamivudine/penciclovir/famciclovir may be admixed, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

Anti-hepatitis B virus nucleoside analogues may be identified by standard methods, such as tests involving studies in *in vitro* primary duck hepatocytye cultures infected

with the duck hepatitis B virus (DHBV). Changes in the levels of preS1 and/or viral DNA in cultures treated with such anologs would indicate activity. Alternatively, analogues may be identified by the ability to interfere with normal acylation of synthetic peptides representing the N-terminal amino acids of DHBV or hepatitis B viruses of man, woodchucks, ground squirrels or other animals.

EXAMPLES

Hepatitis B surface antigen vaccine/Lamivudine pharmacokinetics interaction study in dogs

METHODS

The following vaccine composition was employed. The HBV surface antigen was equivalent to the antigen employed in the commercially available Engerix-B vaccine ™ (Smithkline Beecham Biologicals), except that it was lyophilised.

Lyophilized Ag:	
HBsAg	100µg
Sucrose	12.6 mg
NaCl	20.3mM
NaH_2PO_4 / Na_2HPO_4	1.35 mM
Adjuvant system:	
oil in water emulsion:	250 µl
- Squalene	10.7 mg
- DL α-tocopherol	11.9 mg
- polyoxyethylenesorbitan monooleate (Tween 80)	4.8 mg
Monophosphoryl lipid A	100 µg
QS21	100 µg
Water for injection	q.s. ad 0.5 ml
Na_2HPO_4	575 µg
KH_2PO_4	100 µg
KCl	100 µg
NaCl	4mg
pH	6.8 +/- 0.2

Lamivudine (Zeffix ™, GlaxoWellcome) was administered daily by oral capsule to three male and three female dogs at a dose level of 100 mg/dog/day for 6 weeks. On Days 14, 28 and 42 the HBs/adjuvant vaccine as described above was administered by intramuscular injection immediately before administration of Lamivudine. Blood samples were taken at pre-dose, 0.5, 0.75, 1, 2, 4, 6, 8, 12 and 24 hours after dosing of Lamivudine on Days 7, 14, 28 and 42. The separated plasma was frozen at -20°C prior to despatch to Pharma Bio-Research for analysis of plasma concentrations of Lamivudine.

Sera were collected on days 0, 29 and 43 for anti-HBs antibody evaluation.

RESULTS

Lamivudine pharmacokinetics

Blood samples were taken on Days 7, 14, 28 and 42 of a 6-week toxicity study in order to assess the systemic exposure of male and female dogs to Lamivudine following daily oral administration of Lamivudine at a dose level of 100 mg/dog/day and intramuscular administration of HBs vaccine on Days 14, 28 and 42 immediately before administration of Lamivudine. Plasma concentrations of Lamivudine in samples taken up to 24 hours post-dose were measured by Pharma Bio-Research.

The maximum mean plasma concentrations of Lamivudine occurred at 2 hours post-dose on all the sampling days except for females on Day 7 where the maximum mean plasma Lamivudine concentration occurred at 1 hour post-dose. On Day 28, the maximum mean plasma concentrations of Lamivudine were lower than those values on Day 7, 14 and 42. After the maximum, the mean plasma concentrations of Lamivudine declined in an apparently biexponential manner.

Mean maximum plasma concentrations (Cmax) of Lamivudine and the areas under the plasma Lamivudine concentration-time curves estimated up to 24

hours post-dose (AUC_{24}) on Days 7, 14, 28 and 42 are summarised below with standard deviations in parentheses:

Cmax (ng/ml)

Day 7		*Day 14*		*Day28*		*Day 42*	
Males	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
3045	*4290*	*3176*	*3555*	*2053*	*2542*	*3277*	*3287*
(1516)	*(3335)*	*(871)*	*(1901)*	*(515)*	*(1255)*	*(567)*	*(1256)*

AUC_{24} (ng.h/ml)

Day 7		*Day 14*		*Day 28*		*Day 42*	
Males	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
12541	*11514*	*12858*	*13567*	*11629*	*8883*	*12585*	*11049*
(2211)	*(4324)*	*(3231)*	*(5957)*	*(2694)*	*(2534)*	*(1182)*	*(4334)*

The times at which the maximum plasma concentrations occurred (Tmax) in individual dogs were generally 2 hours, and in the range 0.75 to 4 hours and appeared to be independent of administration of the HBs vaccine.

Plasma concentrations of Lamivudine were quantifiable in male animal numbers 71 and 73 and in female animal number 70 at all time points on Days 7, 14, 28 and 42, therefore, these animals were continuously exposed to quantifiable concentrations of Lamivudine during a dosing interval.

The rate (Cmax) of systemic exposure of female dogs to Lamivudine was slightly higher than that in male dogs. The extent (AUC_{24}) of systemic exposure of female dogs to Lamivudine was generally slightly lower than that in male dogs. However, there was no statistically significant evidence for any sex-related differences in systemic exposure ($p \geq 0.57$).

On Days 14, 28 and 42 the rate (Cmax) and extent (AUC_{24}) of systemic exposure of dogs to Lamivudine were generally similar to those values on Day 7, however, the Cmax values in female dogs on Days 14, 28 and 42 appeared to be lower than those values on Day 7. Overall, there was no statistically significant evidence for any time (day of sampling) related differences in the rate and extent of systemic exposure ($p \geq 0.08$). The mean values of accumulation ratios, based on AUC24 values are summarised below :

	Accumulation ratio	
	Males	**Females**
Day 14/Day 7	1.0	1.2
Day 28/Day 7	0.9	0.8
Day 42/Day 7	1.0	1.0

The mean accumulation ratios were generally close to or less than one indicating that little or no accumulation of Lamivudine occurred following administration of HBs vaccine.

The terminal rate constants, and corresponding terminal half-lives, of Lamivudine on Days 7, 14, 28 and 42 are presented in Tables 5 - 8. The terminal rate constant, where it could be calculated ranged from 0.3239 to 0.1364 $hours^{-1}$ corresponding to a terminal half-life of Lamivudine of 2.1 to 5.1 hours.

Serology

Methodology

Quantitation of anti-HBs antibody was performed by ELISA using HBs (Hep 286) as coating antigen. Antigen and antibody solutions were used at 100 µl per well. Antigen was diluted at a final concentration of 1 µg/ml in PBS and was adsorbed overnight at 4°C to the wells of 96 wells microtiter plates (Maxisorb Immuno-plate, Nunc, Denmark). The plates were then incubated for 1hr 30 min at 37°C with PBS

containing 5% non fat powder milk and 0.1% Tween 20. Two-fold dilutions of sera (starting at 1/50 or 1/200 dilution) in PBS containing 0.5% Gloria milk and 0.1% Tween 20 were added to the HBs-coated plates and incubated for 1 hr at 37°C. The plates were washed four times with PBS 0.1% Tween 20. HRPO-conjugated anti-dog IgG (Rockland, USA) diluted 1/40000 in 0.5% non fat powder milk and 0.1% Tween 20 buffer was added to each well and incubated for 1 hr at RT. After a washing step, plates were incubated for 10 min at RT with a solution of Tetramethyl benzidine (TMB) (Biorad, USA) 2-fold diluted in Citrate buffer (0.1M pH=5.8). The reaction was stopped with H_2SO_4 0.5N and plates were read at 450/630 nm. ELISA titers were expressed as midpoint titers.

Results

The anti-HBs serologic response was measured by ELISA at day 0, 29 and 43. Midpoint titers are presented in the following table :

Midpoint of anti-HBs antibody titers

Dog #	Day 0	Day 29	Day 43
69	25	679	7258
71	25	389	3780
73	25	705	6496
70	25	63	1027
72	25	176	3821
74	25	582	11482
Average	**25**	**383**	**5321**

The mid-point average titers at the different timepoint are the respectively 25 on Day 0 (arbitrary 1/2 of first dilution), 383 on day 29 and 5321 on day 43. This clearly indicate the induction of an immune response.

CONCLUSION

In conclusion, the rate and extent of systemic exposure of dogs to Lamivudine following repeated oral administration of Lamivudine at a dose level of 100 mg/dog/day appeared to be independent of the administration of HBs vaccine on Days 14, 28 and 42 o the 6-week pharmacokinetic interaction study. There was no evidence of a difference in the rate and extent of systemic exposure to Lamivudine between male and female dogs.

Administration of the pharmaccine appeared to be immunogenic and induced high circulating levels of anti-HBs antibodies, validating the use of the Beagle dog as an animal species for this PK interaction study.

CLAIMS

1. A pharmaceutical pack comprising as active ingredients (1) an antiviral agent active against hepatitis B virus and (2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection, the active ingredients being for simultaneous or sequential use.

2. A pharmaceutical pack as claimed in claim 1 for use in the treatment of hepatitis B infections.

3. A pharmaceutical pack as claimed in claim 1 for use in the prevention of hepatitis B infections.

4. A pharmaceutical pack as claimed in any one of the preceding claims wherein the antiviral agent is a nucleoside analogue.

5. A pharmaceutical pack as claimed in claim 4 wherein the antiviral agent is selected from the group comprising; penciclovir, famciclovir or lamivudine.

6. A pharmaceutical pack as claimed in any one of claims 1 – 3 wherein the antiviral agent is a nucleotide analogue.

7. A pharmaceutical pack as claimed in claim 4 or claim 6 wherein the antiviral agent is selected from the group comprising; ganciclovir, lobucavir, adefovir, ribavirin, BMS200,475, vidarabin or ARA-AMP.

8. A pharmaceutical pack as claimed in any one of claims 1 – 3 wherein the antiviral agent is alpha - interferon.

9. A pharmaceutical pack as claimed in any one of the preceding claims wherein the vaccine active against hepatitis B comprises hepatitis B surface antigen.

10. A pharmaceutical pack as claimed in claim 9 wherein the vaccine active against hepatitis B comprises the antigen SL*.

11. A pharmaceutical pack as claimed in claim 9 wherein the vaccine active against hepatitis B comprises the 226 amino acid S antigen.

12. A pharmaceutical pack as claimed in any one of the preceding claims in which the vaccine comprises an adjuvant.

13. A pharmaceutical pack as claimed in claim 12 wherein the adjuvant is selected from the group of adjuvants comprising: 3D-MPL, QS21, a mixture of QS21 and cholesterol, a CpG oligonucleotide, aluminium hydroxide, aluminium phosphate, tocopherol, and an oil in water emulsion or a combination of two or more of the said adjuvants.

14. A pharmaceutical pack as claimed in claim 13 wherein the adjuvant comprises 3D-MPL, QS21 and an oil in water emulsion.

15. A pharmaceutical pack as claimed in claim 14 wherein the oil in water emulsion comprises squalene, tocopherol and polyoxyethylenesorbitan monooleate (Tween 80).

16. A method of treating a patient suffering from or susceptible to Hepatitis B virus infection, comprising administering to a patient in need thereof, either simultaneously or sequentially in any order, a safe and effective amount of 1) an antiviral agent active against hepatitis B virus and 2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection.

17. A method as claimed in claim 13 which comprises the use of a pharmaceutical pack according to any of claims 1 to 15

18. Use of an antiviral compound in the manufacture of a medicament for the treatment of patients already primed with a hepatitis B vaccine and suffering from a hepatitis B virus infection.

19. Use of a hepatitis B vaccine in the manufacture of a medicament for the treatment of patients already primed with an antiviral compound and suffering from a hepatitis B virus infection.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification[7]: A61K 39/29, 31/52, 31/70, 38/21, A61P 5700	A3	(11) International Publication Number: WO 00/41463
		(43) International Publication Date: 20 July 2000 (20.07.00)

(21) International Application Number: PCT/EP99/10295

(22) International Filing Date: 21 December 1999 (21.12.99)

(30) Priority Data:
9900630.6 12 January 1999 (12.01.99) GB

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
9 November 2000 (09.11.00)

(54) Title: COMBINATION OF HEPATITIS B VACCINE WITH ANTIVIRAL AGENTS

(57) Abstract

This invention provides a pharmaceutical pack comprising as active ingredients (1) an antiviral agent active against hepatitis B virus and (2) a vaccine for the prophylaxis and/or treatment of hepatitis B infection, the active ingredients being for simultaneous or sequential use. Preferred components are a nucleoside analogue as the antiviral agent, together with a hepatitis B virus vaccine which comprises a hepatitis B virus surface antigen.

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INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/EP 99/10295

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/29 A61K31/52 A61K31/70 A61K38/21 A61P5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EMBASE, MEDLINE, EPO-Internal, BIOSIS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BONI C ET AL: "Lamivudine treatment can restore T cell responsiveness in chronic hepatitis B 'see comments!." JOURNAL OF CLINICAL INVESTIGATION, (1998 SEP 1) 102 (5) 968-75., XP000909082 abstract; figures 1,3,4 page 969, column 2, paragraph 6 -page 970 page 973, column 2 —— -/—	1-5,9-19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2000	08.08.00

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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